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Case Report

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Cyclosporine induced bradycardia: is it rarely seen?

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ABSTRACT

Immunosuppressive patients experience various side effects from their treatment. Cyclosporine is a commonly prescribed immunomodulatory agent with increasing clinical applications. Although nephropathy is the most common documented side effect, it can cause several cardiac side effects. This report presents a rare side effect of cyclosporine; bradycardia attacks in an immunosuppressed patient.

Keywords: Cyclosporine, cardiovascular toxicity, bradycardia, arrhythmia, syncope

INTRODUCTION

Cyclosporine is a commonly prescribed immunomodulatory agent with increasing clinical applications. The principal application is following solid organ transplantation and certain autoimmune diseases.[1] It has been linked to nephropathy, gingival hyperplasia, and increased hair growth. This report presents a rare side effect of cyclosporine; bradycardia attacks in an immunosuppressed patient.

CASE

A 61-year-old male patient (body weight: 78 kg, height: 1.77 cm) with a history of steroid-resistant immune thrombocytopenic purpura was admitted to the emergency department with syncope. He had no complaints, such as angina, palpitation, or dyspnea. Total loss of consciousness occurred as a sudden and short duration while he was walking, with no prodrome. The patient spontaneously recovered. His past medical history remarks three splenectomy operations, two of which being accessory spleen in 1982, 2015, and 2017. He denied using illicit drugs, mad honey, alcohol, or cigarettes. Before admission, 80 mg methylprednisolone and 50 mg cyclosporine PO were started three weeks ago. Cyclosporine dosage was up-titrated to 100 mg during the first week. He experienced syncope on the second day after the new dose adjustment. During the initial evaluation, blood pressure (BP) was 95/50 mmHg, and heart rate (HR) was 50 bpm. In the initial ECG, sinus bradycardia was detected (PR: 160 ms, HR:50/min, QTc: 402 ms) (**Figure 1**). No abnormality was detected in cardiac and neurologic examination besides the bradycardia. There was no pathology detected in biochemical and hematological parameters. Computed tomography and diffusion magnetic resonance imaging excluded a cerebrovascular incident, trauma, or internal hemorrhage. Transthoracic echocardiography demonstrated a minimal mitral regurgitation with an ejection fraction of 55%. Multiple sinus pauses were revealed in the cardiac telemetry. (**Figure 2**) After intravenous fluid resuscitation and 0.5 mg atropine, BP was increased to 110/60 mmHg, and HR increased to 75 bpm. (**Figure 3**) After a thorough investigation, the adverse drug reaction probability scale (ADR) was calculated as six, and the bradycardia was deemed related to medicine. Although the cyclosporine blood level was calculated as 275 ng/ml, which was in the normal range, the medicine was stopped. Following discharge, 24-hour ambulatory ECG demonstrated a mean HR of 76 bpm, minimum HR of 60 bpm, and a mean QTc of 422 ms, without any significant bradyarrhythmia, and symptoms regressed. The 6th-month follow-up was uneventful.

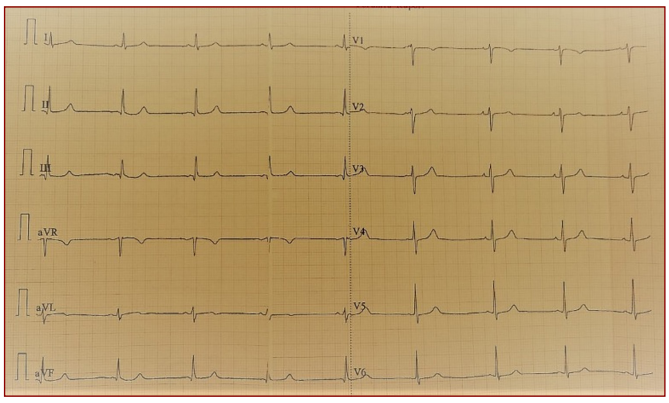

Figure 1. Initial electrocardiography in emergency room demonstrated bradycardia.

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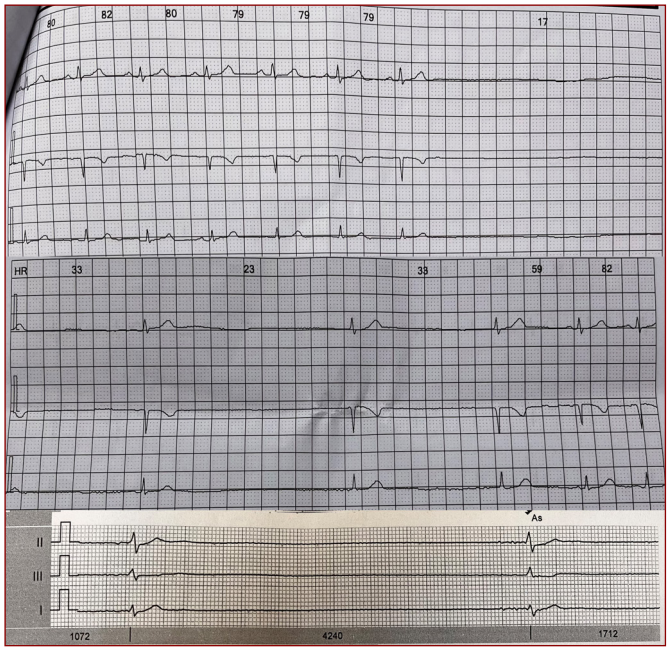

Figure 2: Telemetry records demonstrated multiple sinus pauses.

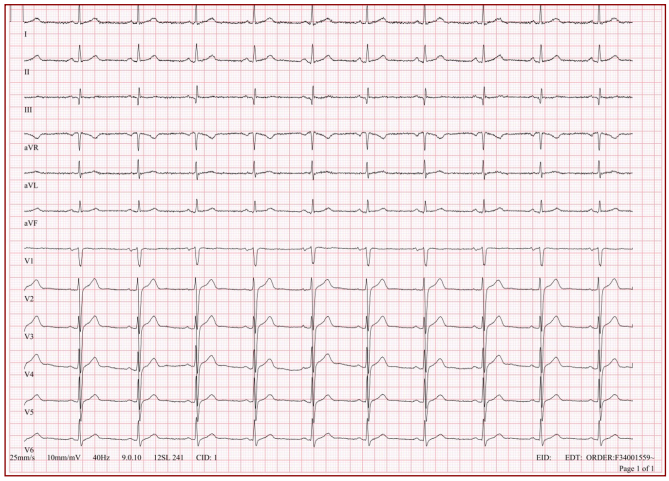

Figure 3: Electrocardiography after the treatment.

DISCUSSION

Cyclosporine is an immunosuppressant drug widely used in transplantation to prevent rejection and treat autoimmune disorders and acts by selective inhibition of the interleukin-2-driven proliferation of activated T-lymphocytes.[2] Nephrotoxicity is the most important; gingival hyperplasia and increased hair growth are clinical side effects. Cardiovascular adverse effects include hypertension and bradycardia after transplantation.[3,4]

In our case, we observed bradycardia attacks caused by the medication. The patient had no structural/arrhythmogenic heart disease and no drug interactions. We used the ADR[5] to assess whether the cause of bradycardia was Cyclosporine. The scale is used to help standardize casualty for all adverse drug reactions, not only for some specific drug classes. We calculated the score as six, the possible ADR in our case.

Moreover, we also performed a search on the Federal Drug Administration Adverse Event Reporting System (FAERS) database.[6] This database is mainly based on individual reports from healthcare professionals or ordinary people who are not healthcare professionals. Although there is a bias possibility due to this mixed nature, it is widely used worldwide and constitutes the most significant side effect database. According to the FAERS database search, only 26 cases were linked to Cyclosporine alone. However, after all of the cases were analyzed, only two of them could be the cause of the bradycardia. As a result, it is safe to say that it is rarely seen.

As our case developed, Cyclosporine induced bradycardia. There are two different mechanisms considered in this setting. The first theory suggests that the drug can suppress nodal automaticity leading to sinus exit block.[7] The following less likely theory suggests bradycardia resulted from the medication's parasympathomimetic activity.[8] The bradycardia side effect was determined as dose-dependent,[4,9] which is consistent with our case. Moreover, steroids, verapamil, diltiazem, and ketoconazole can alter the blood concentration of cyclosporine. Therefore, drug interactions must be considered in every individual, especially when any side effect is encountered. In autoimmune diseases, cyclosporine is used at lower doses compared to post-transplant, and the concentration of cyclosporine in our patient was in the therapeutic range. Even in the therapeutic range, the possibility of side effects, as in our case, should be kept in mind, albeit rarely.

CONCLUSION

Immunosuppressive patients experience various side effects from their treatment. Cardiovascular side effects of their treatment are one of the weighty considerations that can be mistaken. Drug-induced bradycardia must be considered in all patients using cyclosporine in their treatment.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Tedesco D, Haragsim L. Cyclosporine: a review. *J Transplant.* 2012;2012:230386. doi:10.1155/2012/230386
2. Fahr A. Cyclosporin clinical pharmacokinetics. *Clin Pharmacokinet.* 1993;24(6):472-95. doi: 10.2165/00003088-199324060-00004. PMID: 8513650.
3. Textor SC, Canzanello VJ, Taler SJ, Wilson DJ, Schwartz LL, Augustine JE et al. Cyclosporine-induced hypertension after transplantation. *Mayo Clin Proc.* 1994;69(12):1182-1193. doi:10.1016/s0025-6196(12)65772-3
4. Fujisaki G, Kami M, Murashige N, Kishi Y, Inokuchi C, Tanosaki R et al. Sinus bradycardia associated with cyclosporine following allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2005;35(2):211-212. doi:10.1038/sj.bmt.1704747
5. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30(2):239-245. doi:10.1038/clpt.1981.154
6. United States Food and Drug Administration. Adverse Event Reporting System Database (FAERS). https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/6b5a135f-f451-45be-893d-20aaee34e28e/state/analysis. Published 2017. Accessed November 3, 2021.

7. Fujisaki G, Kami M, Murashige N, et al. Sinus bradycardia associated with cyclosporine following allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2005;35(2):211-212. doi:10.1038/sj.bmt.1704747
8. El-Mas MM, Afify EA, Omar AG, Sharabi FM. Cyclosporine adversely affects baroreflexes via inhibition of testosterone modulation of cardiac vagal control. *J Pharmacol Exp Ther.* 2002;301(1):346-354. doi:10.1124/jpet.301.1.346
9. Miller LW. Cardiovascular toxicities of immunosuppressive agents. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg.* 2002;2(9):807-818. doi:10.1034/j.1600-6143.2002.20902.x